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(57) Abstract

A microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system, wherein either the solvent system comprises two hydrophobic solvents, one of which is a hydrophobic alcohol and the second of which is selected from tocol, tocopherols, tocotrienols, and derivatives thereof, or the solvent system comprises two surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil, and the second of which is another water–soluble nonionic surfactant.

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PHARMACEUTICAL MICROEMULSION PRECONCENTRATES COMPRISING CYCLOSPORINS

TECHNICAL FIELD

The invention is directed to pharmaceutical compositions which facilitate the administration of cyclosporins.

BACKGROUND ART

The term "cyclosporin" refers to any member of a class of nonpolar polypeptides, as defined in the Merck Index, Twelfth Edition. One such cyclosporin is cyclosporin A, also known as "cyclosporine" and hereinafter referred to as "cyclosporine", known to be therapeutically active as an immunosuppressant.

Cyclosporins are hydrophobic and have low solubility in aqueous media. This makes it difficult to design pharmaceutical compositions (i.e. dosage forms) comprising cyclosporins which exhibit satisfactory absorption into systemic circulation after oral administration, or absorption into the target tissue upon topical administration.

The cyclosporin can be dissolved in an organic solvent (e.g. ethanol or propylene glycol), but if the solvent is water-miscible, when the composition is mixed with gastrointestinal fluid or other aqueous medium, the cyclosporin will precipitate.

Various methods of overcoming this problem are known in the prior art, but all have certain limitations.

U.S. patent 4388307 discloses compositions comprising cyclosporine in an emulsion preconcentrate that is not water-miscible, but forms an emulsion upon being mixed into gastrointestinal fluids. A commercial product that has been sold under the trademark "Sandimmune" is made according to U.S. patent

4388307, and, more specifically, comprises cyclosporine dissolved in a solvent system comprising ethanol, a vegetable oil and a surfactant. Although this composition was superior to previously known compositions, it still exhibits absorption that is less than the maximum possible and is variable. Also, the use of ethanol has disadvantages, as ethanol is volatile, and the capsules of Sandimmune must be individually packaged in metallic pouches to avoid evaporation of the ethanol.

U.S. patent 5342625 discloses compositions that are said to be superior in certain respects to the compositions of U.S. patent 4388307. The compositions of U.S. patent 5342625 comprise, in addition to the cyclosporin, a hydrophilic phase, a lipophilic (i.e. hydrophobic) phase and a surfactant. The hydrophilic phase is either propylene glycol or a pharmaceutically acceptable alkyl or tetrahydrofurfuryl di- or partial-ether of a low molecular weight mono- or poly-oxy-alkanediol.

The lipophilic phase comprises a solvent which is non-miscible with the hydrophilic phase, and is preferably a fatty acid triglyceride.

It is disclosed that compositions according to U.S. patent 5342625, when added to water, disperse into emulsions with droplet size of less than 2000Å, which is smaller than that obtained with prior art compositions, thus leading to improved absorption.

Emulsions with droplet size of less than 2000Å are defined as "microemulsions". Compositions that, upon addition to water, disperse into microemulsions are called "microemulsion preconcentrates".

A composition made according to the disclosure of U.S. patent 5342625 is now marketed under the trademark "Neoral", in the form of both a soft gelatin capsule containing the microemulsion preconcentrate, and an oral liquid which is a microemulsion preconcentrate intended to be diluted into an aqueous drink before ingestion.

For both the soft gelatin capsules and the oral liquid, the labelling indicates that the "Neoral" emulsion preconcentrate comprises cyclosporine dissolved in ethanol and propylene glycol as hydrophilic solvents, corn oil as lipophilic (hydrophobic) solvent, and polyoxyl 40 hydrogenated castor oil as surfactant. It also contains dl-alpha-tocoperol at a level of about one percent by weight as antioxidant, apparently to prevent oxidation of the corn oil.

While Neoral does enable improved absorption relative to Sandimmune, it still has certain undesirable properties. Specifically:

1. Ethanol is volatile, so that the soft gelatin capsules have to be packaged individually in metallic pouches to prevent evaporation of the ethanol.

2. Ethanol contributes to an undesirable taste of the microemulsion preconcentrate, so that, even after dilution into a sweetened drink, there is still a somewhat unpleasant taste.

3. The concentration of cyclosporine is limited to about 100 mg per mL so that a soft gelatin capsule containing 100 mg of cyclosporine is larger than desirable and difficult to swallow.

International Publication Number W094/25068 discloses improved compositions in the form of microemulsion preconcentrates in which the principal solvent for the cyclosporin is an alcohol which is selected from alcohols having a boiling point above 100°C and a solubility in water of under 10 g per 100 g at 20°C. Such alcohols are referred to as hydrophobic alcohols.

Preferred hydrophobic alcohols, within the scope of the disclosure of W094/25068, are saturated alkyl alcohols having 8 to 14 carbon atoms per molecule, including 1-octyl, 2-octyl, 1-decyl, 1-dodecyl and 1-tetradecyl alcohols. Preferred surfactants for use along with the hydrophobic alcohol are polyoxethylene glycolated natural or hydrogenated vegetable oils.

New Zealand Patent Application No. 280689 discloses improved microemulsion preconcentrates in which a cyclosporin is dissolved in a solvent system comprising a hydrophobic component, a hydrophilic component and a surfactant, wherein the hydrophobic component is selected from tocol, tocopherols and tocotrienols, and derivatives thereof.

The preferred surfactants are again polyoxyethylene glycolated natural or hydrogenated vegetable oils.

Although the compositions of International Publication Number W094/25068 and New Zealand Patent Application No. 280689 provide certain advantages relative to Neoral, they still have certain limitations. Specifically, it has been found that, despite the advantages of compositions within the scope of these disclosures, it is difficult to achieve a microemulsion with droplet size as small as is achieved with Neoral, with the result that it is difficult to achieve, upon oral administration, absorption into systemic circulation as good as that achieved with Neoral.

Furthermore, it has been found that, with these compositions, the quantity of the preferred surfactant (i.e. a polyoxyethylene glycolated natural or hydrogenated vegetable oil) required to get a satisfactory microemulsion preconcentrate is higher than desired, giving rise to toxicity concerns.

It is thus an object of the within invention to enable compositions with the advantages of compositions disclosed in International Publication Number W094/25068 and New Zealand Patent Application No. 280689 and also enable improved microemulsion fineness.

It is also an object of the within invention to enable compositions with improved microemulsion fineness using reduced quantities of the preferred surfactant.

SUMMARY OF THE INVENTION

The term "solvent system" as used herein is to be understood to mean the carrier in which the drug (i.e. a cyclosporin) is dissolved. The solvent system may be a single solvent or a combination or a mixture of ingredients included as solvents, surfactants, diluents, or for other purposes.

As aforesaid, International Publication W094/25068 discloses use of a hydrophobic alcohol as the hydrophobic solvent in the composition, and New Zealand Patent Application No. 280689 discloses the use of a component selected from tocol, tocopherols and tocotrienols and derivatives thereof as hydrophobic solvent.

It has now surprisingly been found that these two types of hydrophobic solvents act synergistically, so that a combination of them enables compositions that will disperse into microemulsions of smaller droplet size than can be achieved with either component alone as hydrophobic solvent.

Furthermore, as aforesaid, both International Publication W094/25068 and New Zealand Patent Application No. 280689 disclose that polyoxyethylene glycolated natural or hydrogenated vegetable oils are preferred surfactants.

It has now surprisingly been found that these surfactants act synergistically with other water-soluble nonionic surfactants, with the result that part of the polyoxyethylene glycolated natural or hydrogenated vegetable oil can be replaced by another water-soluble nonionic surfactant as cosurfactant, without increasing the total amount of surfactant and without loss of effectiveness in enabling dispersion into a microemulsion of small droplet size.

Accordingly, one aspect of the invention is the use of a solvent system comprising two hydrophobic solvents, one of which is a hydrophobic alcohol and the second of which is selected from tocol, tocopherols and tocotrienols and derivatives thereof. Also, a second aspect of the invention is the use of a combination of two surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil and the second of which is another water-soluble nonionic surfactant.

More particularly, the invention is a microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system, wherein said solvent system further comprises at least one hydrophobic solvent and at least one surfactant, and wherein either:

1) the solvent system comprises two hydrophobic solvents, one of which is a hydrophobic alcohol and the second of which is selected from tocol, tocopherols, tocotrienols, and derivatives thereof, or

2) the solvent system comprises two water-soluble nonionic surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.

DETAILED DESCRIPTION OF THE INVENTION

A microemulsion preconcentrate comprising a cyclosporin must contain at least one hydrophobic solvent, at least one surfactant, also preferably at least one hydrophilic solvent.

A hydrophobic solvent is needed because, if the cyclosporin is dissolved in only a hydrophilic solvent, then when the composition is mixed into an aqueous medium, the hydrophilic solvent will dissolve in the water, causing precipitation of the cyclosporin.

A surfactant is needed to enable the composition (i.e. the microemulsion preconcentrate) to disperse into a microemulsion when added to water.

It is also necessary that the solvents used in the composition have adequate capacity to dissolve the cyclosporin and to keep it dissolved without precipitation during long term storage.

The aforementioned hydrophobic solvents are not very good solvents for cyclosporine. Accordingly, if only hydrophobic solvents are used, the quantity needed is larger than desirable. The quantity can be decreased by including in the composition some quantity of a hydrophilic solvent that is a better solvent for the cyclosporin.

Ethanol can be used as the hydrophilic solvent, but ethanol has the disadvantage of being volatile. Preferred hydrophilic solvents that are less volatile are propylene glycol, propylene carbonate, benzyl alcohol, and low molecular weight polyethylene glycols in the range of less than about 1000.

As aforesaid, one aspect of the invention is the use of a solvent system comprising two hydrophobic solvents, one of which is a hydrophobic alcohol, and the second of which is selected from tocol, tocopherols, and tocotrienols and derivatives thereof.

The term "hydrophobic alcohol" as used hereinafter shall be understood as meaning a monoalcohol having a solubility in water of under 5 g per 100 g at 20°C.

Preferred hydrophobic alcohols are saturated alkyl alcohols having from 8 to 16 carbon atoms per molecule.

Most preferred are 1-dodecyl alcohol (also known as lauryl alcohol) and 1-tetradecyl alcohol (also known as myristyl alcohol).

The term "tocopherols" as used herein is to be understood to mean any one of or a mixture of any of the compounds which can be regarded as a substituted tocol and is identified as a type of tocopherol in the Merck Index Twelfth Edition at entry numbers 9632 to 9638 inclusive and entry number 10159, specifically including alpha-, beta-, delta- and gamma-tocopherol.

Alpha-tocopherol is also known as Vitamin E.

The term "tocotrienol" as used herein shall be understood to mean any one of or a mixture of alpha-, beta-, delta- and gamma-tocotrienol. Tocotrienols are similar to tocopherols but have an unsaturated side chain consisting of three double bonds.

The term "derivative" will be understood to mean any compound that can be formed by a reaction with any compound selected from tocol, tocopherols and tocotrienols. Derivatives will thus include, for example, tocol acetate, and alpha-tocopheryl acetate.

Some or all of tocol, the tocopherols and the tocotrienols, and derivatives thereof are available as different stereoisomers, and it will be understood that the different stereoisomers or mixtures thereof are included within the definition.

From among tocol, tocopherols, tocotrienols and derivatives thereof the preferred choices are alpha-tocopherol and natural mixed tocopherols.

Especially preferred is natural mixed tocopherols. These are available, for example, as products sold under the tradenames Tenox GT-2 by Eastman Chemical Products Inc. and Covi-Ox T-70 by Henkel Corporation.

Tenox GT-2 and Covi-Ox T-70 both are comprised of about 70% total tocopherols and 30% vegetable oil. The total tocopherol content in these products is made up of approximately 12% to 14% d-alpha, 62% to 65% d-gamma, 23% to 24% d-delta and 1% d-beta.

As aforesaid, a second aspect of the invention is the use of a combination of two surfactants, the first of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil; for example, polyoxyethylene glycolated natural or hydrogenated castor oil. Particularly suitable are the products designated in the United States Pharmacopoeia and National Formulary as Polyoxyl 35 Castor Oil and Polyoxyl 40 Hydrogenated Castor Oil, which are available under the tradenames Cremophor EL and Cremophor RH40 respectively.

The second surfactant is another water-soluble nonionic surfactant. Preferred as the second surfactant are polyoxyethylene-sorbitan-fatty acid esters; e.g. mono- and tri-lauryl, palmityl, stearyl and oleyl esters; e.g. products of the type known as polysorbates and commonly available under the tradename "Tween". Especially preferred is polyoxyethylene 20 sorbitan monolaurate, which is also known as polysorbate 20.

While the two aspects of the invention may be used independently of each other, it is preferred to use them together. Preferred compositions are thus compositions which comprise all of the following:

1. a cyclosporin
2. a hydrophobic alcohol
3. a compound selected from tocol, tocopherols, tocotrienols, and derivatives thereof.
4. a polyoxyethylene glycolated natural or hydrogenated vegetable oil
5. a second water-soluble nonionic surfactant
6. a hydrophilic solvent

Compositions in accordance with the invention may also contain other ingredients.

For example, the composition may include, in addition to the foregoing, one or more other ingredients that are included as diluents, thickening agents, anti-oxidants, flavouring agents, and so forth.

Compositions in accordance with the invention may be liquids at ambient temperature or they may be solids prepared, for example, by use of one or more ingredients with melting point above ambient temperature. The ingredients may be blended at a temperature above the melting point and then used to fill capsules while still molten, or cooled to form solids. The solids may be ground into granules or powder for further processing; for example, filling capsules or manufacture of tablets.

If it is desired to increase the melting point to ensure that the composition is a solid at room temperature, this may be accomplished by adding a further ingredient with a relatively high melting point, such as, for example, polyethylene glycol with average molecular weight of above 1000.

Capsules or tablets may be further processed by applying coatings thereto.

Compositions in accordance with the invention may comprise dosage forms for direct administration as microemulsion preconcentrates. For example the microemulsion preconcentrate may be directly used as liquid for oral ingestion, parenteral use, or topical application or it may be encapsulated into gelatin capsules for oral ingestion.

However, the present invention also provides pharmaceutical compositions in which the microemulsion preconcentrate is further processed into a microemulsion. Thus where oral administration is practised, microemulsions obtained, e.g. by diluting a microemulsion preconcentrate with water or other aqueous medium (for example, a sweetened or flavoured preparation for drinking), may be employed as formulations for drinking. Similarly, where topical application is intended, compositions comprising a microemulsion preconcentrate, a thickening agent, and water will provide an aqueous microemulsion in gel, paste, cream or like form.

Compositions in accordance with the present invention, whether microemulsion preconcentrates or microemulsions, may be employed for administration in any appropriate manner and form; e.g. orally, as liquids or granules or in unit dosage form, for example in hard or soft gelatin encapsulated form, parenterally or topically; e.g. for application to the skin; for example in the form of a cream, paste, lotion, gel, ointment, poultice, cataplasm, plaster, dermal patch, powder, topically applicable spray, or the like, or for ophthalmic application; for example in the form of an eye-drop, lotion or gel formulation. Readily flowable forms may also be employed; e.g. for intralesional injection for the treatment of psoriasis, or may be administered rectally. Compositions in accordance with the invention are, however, primarily intended for oral or topical application, including application to the skin or eyes.

The relative proportion of the cyclosporin and other ingredients in the compositions of the invention will, of course, vary considerably depending on the particular type of composition concerned; e.g. whether it is a microemulsion preconcentrate or microemulsion, the route of administration, and so forth. The relative proportions will also vary depending on the particular ingredients employed and the desired physical characteristics of the composition, e.g. in the case of a composition for topical use, whether this is to be a free flowing liquid or a paste. Determination of workable proportions in any particular instance will generally be within the capability of persons skilled in the art.

The invention will be more fully understood by the following examples which are illustrative but not limiting of compositions in accordance with the present invention.

EXAMPLES

In each of the following examples, the ingredients were weighed into a test tube in the proportions shown, the test tubes and contents were warmed to 100°C in a water bath, and then the test tubes were shaken until the contents of each tube were interdissolved to form a clear solution.

Then 1 g from the composition in each test tube was transferred to another test tube, 20 mL of warm (37°C) water was added, and the test tube was shaken to disperse the 1 g of the composition in the water to form an emulsion or microemulsion. The resultant emulsions or microemulsions were then compared for clarity by measuring the light transmittance through a 1 cm at 600 nm. A higher transmittance indicates a smaller droplet size and hence, a finer emulsion or microemulsion.

Example No.:	1	2	3	4	5	6
Cyclosporine	1.0	1.0	1.0	1.0	1.0	1.0
1-tetradecyl alcohol	1.4	1.3	1.2	0.8	0.4	0
Covi-Ox T-70	0	0.1	0.2	0.6	1.0	1.4
Propylene Carbonate	1.0	1.0	1.0	1.0	1.0	1.0
Cremophor RH40	3.0	3.0	3.0	3.0	3.0	3.0
Polysorbate 20	2.4	2.4	2.4	2.4	2.4	2.4
Total:	8.8	8.8	8.8	8.8	8.8	8.8
Transmittance at 600 nm	64.4%	89.0%	94.8%	95.2%	93.6%	65.8%

As aforesaid, the transmittance is that of an emulsion or microemulsion made by dispersing 1 g of the composition in 20 mL of warm water. It can be seen that the transmittance is only about 65% when either 1-tetradecyl alcohol or Covi-Ox-T-70 is used alone as hydrophobic solvent, but the transmittance improves substantially in examples 2 to 5, when a combination of the two is used.

Example No.	7	8	9	10	11	12
Cyclosporine	1.0	1.0	1.0	1.0	1.0	1.0
1-tetradecyl alcohol	1.2	1.2	1.2	1.2	1.2	1.2
Covi-Ox T-70	0.2	0.2	0.2	0.2	0.2	0.2
Propylene Carbonate	0.8	0.8	0.8	0.8	0.8	0.8
Cremophor RH40	5.2	4.2	2.8	1.8	1.0	0
Polysorbate 20	0	1.0	2.4	3.4	4.2	5.2
Total:	8.4	8.4	8.4	8.4	8.4	8.4
Transmittance at 600 nm	69.8%	93.8%	94.2%	63.3%	3.3%	0.0%

The high opacity (low transmittance) obtained with a dispersion of the composition of example 12 in water shows that Polysorbate 20 when used alone is ineffective as a surfactant in the composition.

The higher transmittance obtained with example 7 shows that Cremophor RH40 (Polyoxyl 40 Hydrogenated Castor Oil) when used alone as the surfactant is much superior to Polysorbate 20.

Examples 8 and 9 demonstrate that an even higher transmittance and thus a finer microemulsion can be obtained by using a combination of the two surfactants instead of using Polyoxyl 40 Hydrogenated Castor Oil alone.

As a basis for comparison, 1 g of the marketed product, Neoral Oral Solution, was similarly dispersed in 20 ml of warm (37°C) water and the transmittance through 1 cm at 600 nm was measured to be 83.9%. The composition of examples 2, 3, 4, 5, 8, and 9 all gave higher transmittance than Neoral, which indicates that the microemulsions are at least as fine as obtained with Neoral.

WHAT IS CLAIMED IS:

1. A microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system, wherein said solvent system further comprises at least one hydrophobic solvent and at least one surfactant, and wherein either:

a) the solvent system comprises two hydrophobic solvents, one of which is a hydrophobic alcohol and the second of which is selected from tocol, tocopherols, tocotrienols, and derivatives thereof, or

b) the solvent system comprises two water-soluble nonionic surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.

2. A microemulsion according to Claim 1 wherein the solvent system further comprises a hydrophilic solvent selected from ethanol, propylene glycol, propylene carbonate, benzyl alcohol and polyethylene glycol.

3. A microemulsion preconcentrate comprising a cyclosporin dissolved in a solvent system comprising a hydrophobic alcohol, a second hydrophobic solvent selected from tocol, tocopherols, tocotrienols and derivatives thereof, and at least one surfactant.

4. A microemulsion according to Claim 3 wherein the solvent system further comprises a hydrophilic solvent selected from ethanol, propylene glycol, propylene carbonate, benzyl alcohol and polyethylene glycol.

5. A composition according to claim 3 or 4 wherein the hydrophobic alcohol is selected from 1-dodecyl alcohol and 1-tetradecyl alcohol.

6. A composition according to claim 3, 4 or 5 wherein the second hydrophobic solvent is selected from tocopherols.

7. A composition according to claim 3, 4 or 5 wherein the second hydrophobic solvent is Vitamin E.

8. A composition according to claim 3, 4 or 5 wherein the second hydrophobic solvent is natural mixed tocopherols.

9. A microemulsion preconcentrate comprising a cyclosporin dissolved in solvent system wherein said solvent system comprises at least one hydrophobic solvent, and two water-soluble nonionic surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.

10. A microemulsion according to Claim 9 wherein the solvent system further comprises a hydrophilic solvent selected from ethanol, propylene glycol, propylene carbonate, benzyl alcohol and polyethylene glycol.

11. A composition according to claim 9 or 10, wherein the second surfactant is a polyoxyethylene-sorbitan-fatty acid ester.

12. A composition according to claim 9 or 10, wherein the second surfactant is polysorbate 20.

13. A composition according to any of claims 9 to 12, wherein the polyoxyethylene glycolated natural or hydrogenated vegetable oil is a polyoxyethylene glycolated natural or hydrogenated castor oil.

14. A composition according to any of claims 9 to 13, wherein the hydrophobic solvent is selected from tocol, tocopherols, tocotrienols or derivatives thereof.

15. A composition according to any of claims 9 to 13, wherein the hydrophobic solvent is selected from tocopherols.

16. A composition according to any of claims 9 to 13, wherein the hydrophobic solvent is Vitamin E.

17. A composition according to any of claims 9 to 13, wherein the hydrophobic solvent is natural mixed tocopherols.

18. A composition according to any of claims 3 to 8, wherein the solvent system comprises two water-soluble nonionic surfactants, one of which is a polyoxyethylene glycolated natural or hydrogenated vegetable oil.

19. A composition according to claim 18, wherein the second surfactant is a polyoxyethylene-sorbitan-fatty acid ester.

20. A composition according to claim 18, wherein the second surfactant is polysorbate 20.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/CA 98/00023

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K38/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 62 019 512 A (SHISEIDO) 28 January 1987 see examples 1-3	1-4,6,7
X	US 5 589 455 A (WOO JONG S) 31 December 1996 see abstract see column 1, line 7-19 see column 6, line 7-29 see example 1	9-13
X	EP 0 711 550 A (HANMI PHARM IND CO LTD) 15 May 1996 see abstract; examples see page 2, line 7-14 see page 5, line 13-24	9,11-13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 March 1998	06/04/1998

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/CA 98/00023

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 218 334 A (SANDOZ LTD) 15 November 1989 see abstract see page 5, line 3-5 see page 9, line 14 see page 9, line 24 - page 10, line 5 see page 10, line 32-33	1-20

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interi ıal Application No
PCT/CA 98/00023

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62019512 A	28-01-87	NONE	
US 5589455 A	31-12-96	NONE	
EP 0711550 A	15-05-96	CN 1128671 A	14-08-96
		JP 8310964 A	26-11-96
		US 5603951 A	18-02-97
GB 2218334 A	15-11-89	BE 1002266 A	13-11-90
		CH 679119 A	31-12-91
		DE 3915617 A	16-11-89
		FR 2631235 A	17-11-89
		JP 1977742 C	17-10-95
		JP 2017127 A	22-01-90
		JP 7005473 B	25-01-95